to col. 7, line 5). The process is repeated until the cumulative hybridization data is consistent with only a single target sequence (col. 7, lines 9-15).

The Examiner takes the view that Skiena differs from the present claims only in that Skiena does not teach using a target sequence that is a variant of a known reference sequence. Applicants, however, submit that there are several additional distinctions.

With respect to step (a) of present claim 1 reciting designing an array of probes to comprise a probe set complementary to a known reference sequence, the Examiner takes the view that such is disclosed by Skiena citing to the abstract, Table 1, column 2, lines 20-27 and claim 1a of Skiena. However, none of these sources makes any mention of designing an array of probes to comprise a probe set complementary to a known reference sequence. Rather, Skiena's initial array is a universal sequencing chip containing all probes of a given length (col. 2, lines 23-24). By definition, such an array contains all probes of a given length, and is not designed with respect to a reference sequence.

With respect to step (c) of claim 1 referring to estimating the sequence of a target nucleic acid, the Examiner takes the view that such is disclosed by steps (c) and (d) of claim 1 of Skiena. However, neither of these steps recites "estimating" a sequence. Indeed the Examiner will not find the word "estimating" in the entire Skiena patent. Rather claim 1c requires identifying a set of hybridizing oligonucleotides, and step (d) recites selecting a second set of oligonucleotides based on the hybridization of the first set. Neither step (c) or (d) refers in any way to the reconstruction of an estimated sequence from the set of positively hybridizing oligonucleotides. To say that a set of positively hybridizing oligonucleotides itself constitutes a sequence without any attempt being made to orient the oligonucleotides with respect to each other would be akin to saying that a restriction mapping of a target reveals its sequence. Such would be abhorrent to typical usage in the art whereby a restriction map or set of hybridizing oligonucleotides may be regarded as being a fingerprint but is not a sequence.

With respect to step (h) of claim 1, referring to reestimating the sequence of a target nucleic acid, the Examiner takes the view that such is disclosed by claims 1h and 2

of Skiena. However, these claims refer to "determining" the sequence of a target not reestimating. In Skiena's initial iterations of his method, he does not disclose estimating a target sequence but rather identifies a subset of hybridizing probes. In the final step of Skiena's method he does not estimate a target sequence, but rather determines the sequence uniquely. In Skiena's view at least, the determined sequence is correct and not an estimated, much less a reestimated sequence (col. 7, lines 12-15).

With respect to claim 2, referring to repeating steps (e) and (h) as necessary until the reestimated sequence is constant between successive cycles of the method, the Examiner takes the view that such is disclosed by claim 2 of Skiena. However, claim 2 refers to determining a target sequence based on sets of hybridizing probe sets from iterations of his method. In Skiena's method, all cycles but the last determine different subsets of hybridizing probes. The last cycle determines a unique target sequence. There is no mention of estimating target sequences in any cycle, much less of performing the method until an estimated target sequence remains constant.

With respect to claim 15, referring to designing an array of probes to be complementary to an estimated sequence of the target nucleic acid, the Examiner takes the view that such is disclosed by Figs. 2 and 3 and claims 3-14 of Skiena. Regarding Fig. 2, this Figure is given to illustrate deficiencies in the prior art (see col. 3, lines 28-48) rather than Skiena's own method. Fig. 3 illustrates the number of iterations of Skiena's method required until a unique sequence can be determined from the hybridization data. It says nothing about designing probes to an estimated sequence. Likewise, claims 3-14 do not mention an estimated sequence, much less designing probes to it. To reiterate, Skiena's initial array is a universal sequencing array, and subsequent arrays are designed by combining sequences from probes that hybridize to the target sequence, not by their complementarity to an estimated sequence.

The secondary reference Futreal reference does not remedy any of the above noted deficiencies. The reference is apparently cited to establish that target sequences that are variants of a reference sequence are known to exist and it is useful to analyzed them with probe based assays. However, merely performing Skiena's method with a

target sequence that happens to be a variant of a known reference sequence does not give rise to the presently claimed invention.

Not only would one have to perform Skiena's method with a target sequence that is a variant of a known reference sequence, one would at the very least have to discard Skiena's own strategy of starting with a universal sequence array containing all probes of a given length in favor of designing an array to comprise a set of probes having complementarity to the known reference sequence. To do so would forfeit the utility of Skiena's own method for an analyzing any kind of target sequence. Moreover, the remaining steps in Skiena method which are intended for analyzing a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence. The secondary reference merely indicates the well-known fact that target sequences that are variants of known reference sequences exist ; it does not provide any suggestion to modify the strategy for analyzing target sequences proposed by Skiena, and particularly not in a way that forfeits the principal advantage of Skiena's method. Furthermore, the secondary reference does not remedy any of the other deficiencies in Skiena noted above.

Claims 1-2 and 5-15 stand rejected as obvious over Skiena in view of Fureal in further view of Cronin. Skiena and Futreal are applied as above. The Examiner acknowledges that that these references do not teach various details of the reference sequences and probe sets specified in the present claims. The Examiner takes the view that these details are described by Cronin. The Examiner takes the view that it would have been obvious to combine the teaching of Cronin with the other references in view of Cronin's statement that her method provides strategies for comparing a target sequence and a reference sequence. This rejection is respectfully traversed.

The above claims are distinguished over Cronin, Futreal and Skiena for at least the same reasons as discussed above with respect to Skiena and Futreal alone. In addition, applicants submit that there was no motivation to combine Cronin with Skiena. The motivation identified by the Examiner provides reason to perform Cronin's methods as written but not to modify them. The Examiner also ignores the fact that Cronin's

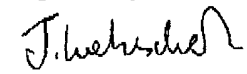
strategy of probe design could not be incorporated into Skiena's method without changing much of Skiena's own method and forfeiting most of its advantages. For example, if one employed Cronin's strategy of selecting probe sets by complementarity to a known reference sequence, then one would have to discard Skiena's alternative strategy of using a universal sequence array, and with it, the attendant advantages of being able to analyze any target sequence. It is also unclear why one would employ Skiena' strategy of designing secondary arrays if the primary array were that of Cronin rather than a universal array as described by Skiena. As noted above, Skiena's strategy for designing a secondary array is adapted to analyze a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence.

For these additional reasons, it is submitted that claims 1-2 and 5-15 are distinguished.

Claims 1-6 and 15 stand rejected as obvious over Skiena in view of Futreal in further view of Horwitz. Skiena and Futreal are cited as above. Horwitz is cited as teaching species variants of HIV. The above claims are distinguished over the combination of Skiena, Futreal and Horwitz for at least the same reasons that they are distinguished over Skiena and Futreal alone.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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